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Recent Penile Sexual Contact is Associated with an Increased Odds of High-Risk Cervical Human Papillomavirus Infection in Transgender Men

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Abstract

Background: Transgender men (TM) have a male, masculine, or non-female gender identity, yet were assigned female sex at birth on the basis of their external genitalia. The majority of TM are at-risk of infection with one of several high-risk strains of the human papillomavirus (hr-HPV), acquired primarily through sexual contact, that cause 99.7% of cervical cancers. This study aimed to explore the association between sexual behaviors and current cervical hr-HPV infection in TM with a cervix.

Methods: The primary aim of this analysis was to test for an association between participant self-report of sexual contact with a penis in the past 1 year and current infection with cervical hr-HPV as measured by provider-collected cervical HPV DNA assay. This is a secondary analysis of a bio-behavioral sexual health study conducted at a health center in Boston, MA from 2015–2016. Analysis was conducted using logistic regression with significance level set at $p < 0.05$; the primary analysis was adjusted for self-reported age, current tobacco use, years of testosterone use, and HPV vaccination status.

Results: Overall prevalence of hr-HPV was 15.9%. In adjusted analyses, participants reporting receptive penile vaginal sex with any of their most recent 3 sexual partners in the past 12 months

had more than 5 times greater odds of current hr-HPV infection than those reporting no penile sex of any kind during this timeframe (Odds Ratio=5.23, 95% Confidence Interval=1.61–17.02).

Conclusion(s): Vaginal-receptive penile sex in the last 12 months was associated with a five-fold increased odds of cervical high-risk HPV infection among TM. Findings can inform future population level study of associations between sexual behaviors and hr-HPV risk, which could lead to more individualized approaches to screening.

Short Summary:

A study of cervical cancer screening in transgender men in Boston, MA found those who reported receptive penile-vaginal sex with at least one of their most recent three sexual partners in the past year had more than 5 times the odds of a current high-risk cervical HPV infection as were those reporting no receptive vaginal sex in this same time frame.

Keywords

Cervical Neoplasms; Transgender Persons; Papillomaviridae; Sexuality

INTRODUCTION

Transgender men and transmasculine non-binary people (collectively for this manuscript: TM) have a male, masculine, or non-female gender identity, yet were assigned female sex at birth on the basis of their external genitalia. While many transgender people seek gender-affirming surgical interventions, access to these treatments varies widely; (1–3) only 1 in 5 TM has undergone hysterectomy, and 1 in 4 TM report no desire for the procedure.(4) Pregnancies carried by TM are becoming more well-known; (5,6) this combined with a lack of evidence supporting a medical basis alone for hysterectomy in TM may result in even more TM retaining their cervix, and therefore necessitating ongoing, routine cervical cancer screening. (7)

As with any person with a uterine cervix, TM may acquire an infection with one of the 13 high-risk strains of the human papillomavirus (hr-HPV) that cause 99.7% of cervical cancers; these infections are acquired primarily through sexual contact. (8–11) TM experience reduced rates of screening for cervical cancer. In one study based at a health center specializing in transgender care, TM were 37% less likely to be current for cervical cancer screening as compared to cisgender (non-transgender) women.(12) Numerous factors contribute to this disparity; one in four TM avoid preventive care due to discrimination,(4) two in five transgender people report delaying healthcare of any kind due to prior discrimination or disrespect, (4) and one in seven TM report being denied cervical cancer screening by their provider. (13) Additionally, TM are 10 times as likely as cisgender women to have had an inadequate Pap specimen, and are subsequently less likely than cisgender women to return for follow-up care to achieve a satisfactory result (53% vs 68%). (14) Discomfort during cytology sampling is another key driver of cervical cancer screening disparities; speculum exams can be physically painful for TM, due to prior history of sexual assault or other trauma, acute emotional distress from undergoing a gender-discordant, “female” exam, or testosterone-induced vaginal atrophy.(15–19) Current US cervical cancer

screening guidelines emphasize screening for “women” rather than “people with a cervix” and may lead patients and providers to believe that cervical cancer screening is not necessary for TM. (8,20,21)

TM have a wide range of sexual orientations and behaviors, placing them at varying risk of cervical hr-HPV infection.(22) As many as two-thirds of TM identify as gay men and are sexually active with other men.(23,24) TM who have not undergone vaginectomy may continue to engage in vaginal sex, and one study found that 36% of TM reported condomless receptive vaginal sex with a partner’s penis in the past 12 months.(25) Given this diversity in sexual behavior and therefore potential variability in hr-HPV risk, TM would benefit from efforts to increase screening uptake. However, US Preventative Services (USPSTF) Guidelines make no mention of TM; they do recommend either 1) cytologic (Papanicolaou) screening every 3 years for *women* ages 21–65 who have a cervix, with optional co-testing for hr-HPV in *women* ages 30–65 (which extends the screening interval to five years), or 2) primary hr-HPV screening for *women* ages 30–65, with positive results further evaluated by cytology or colposcopy. (20)

Because sexually transmitted hr-HPV infection is the primary risk factor for cervical cancer, we aimed to explore the association between cervical hr-HPV infection in TM people through this secondary analysis of a previously reported preventive and sexual health screening study in TM adult patients. (26) Our goal is to better understand the actual risk present in this population to both support inclusion of TM In future guidelines, as well as explore the possibility of a more personalized, risk-based approach to screening for those found to be at the lowest risk.

MATERIALS AND METHODS

Between March 2015 and September 2016, 150 TM individuals were enrolled via convenience sampling in a biobehavioral sexual health study, based at a health center in Boston, MA that specializes in the care of sexual and gender minorities; methods and main findings have been previously reported (27). Participants were eligible to participate in the study if they met the following criteria: (1) ages 21 to 64 years; (2) assigned a female sex at birth and now have a masculine spectrum gender identity; (3) cervix present; (4) sexually active within the past 3 years (sexual partner(s) of any gender); (5) able to speak and understand English; and (6) willing and able to provide informed consent. Participants were provided with a \$100 incentive upon completion of the study activities. All study activities were approved by the Institutional Review Board at Fenway Health, in Boston, MA.

Participants completed a survey which included self-reported demographics (i.e., age, race/ethnicity, gender identity, educational attainment, employment status, housing stability, relationship status, gender of partners in the past 12 months, and HIV status); years on hormones, HPV vaccination status, and tobacco use. Participants were also asked to report whether or not they had engaged sex acts involving a penis in the last 12 months with up to 3 of their most recent sexual partners; responses were categorized as: No sexual contact of any type; sexually active but no sexual contact with a penis, sexual contact (i.e. oral, anal) with a penis but without vaginal receptive sex, and sexual contact with a penis that was inclusive of

vaginal receptive sex. It should be noted that while the term “vaginal” is used throughout this manuscript, some TM use the term “frontal” when referring to the vaginal area (28).

Sample collection occurred in an exam room by a physician or nurse practitioner. Prior to collecting biological specimens, providers conducted a brief pre-exam sexual health history using a standardized script of questions. Cervical specimens were collected using a Medscand® Pap-Perfect® Spatula and Cytobrush Plus (Cooper Surgical, Trumbull, CT, USA) which was deposited into a Cytyc® ThinPrep® solution canister. This sample was sent for cytologic analysis using the Bethesda System terminology (Quest Diagnostics, Marlborough, MA, USA), as well as for a DNA Hybridization Assay for 13 high-risk HPV types associated with cervical cancer using Digene Hybrid Capture II® technology (Qiagen Gaithersburg, Inc., Gaithersburg, MD, USA) (29). The hr-HPV assays returned a qualitative positive or negative result for the presence of any one of the 13 high-risk types, without identifying the specific oncogenic subtype. Additionally, rapid HIV tests were performed to verify self-reported HIV status.

Data Analysis

The primary aim of this analysis was to test for an association between participant self-report of sexual contact with a penis with up to 3 of the participants most recent sexual partners in the past 12 months (primary independent variable) and current infection with cervical hr-HPV (outcome) using the results of a provider-collected cervical hr-HPV DNA assay, among the group of participants who reported sexual activity of any kind in the prior 12 months. The use of last 3 sex partners in the past 12 months, rather than longer historical or lifetime periods, was based on the limitations of the questionnaire used in the parent study from which this secondary analysis was conducted.

Statistical analysis was conducted using SAS statistical software version 9.14. Descriptive statistics (means and frequencies) were used to examine participant demographics as well as the primary independent variable (sexual risk behavior) and covariates, overall and stratified by the study outcome (hr-HPV DNA status). Bivariate and adjusted logistic regression models were used to calculate an odds ratio to describe the association between sexual risk behavior in the past 12 months among sexually active participants (primary independent variable: no sexual contact with a penis [referent]; sexual contact (i.e. oral, anal) with a penis but without vaginal receptive sex; and sexual contact with a penis that was inclusive of vaginal receptive sex) and provider-collected cervical hr-HPV DNA (outcome). Participants who were not sexually active at all in the past 12 months ($n = 8$) or who did not report their sexual behavior for this time frame ($n = 1$) were excluded from the logistic regression analyses as all of these participants tested negative for hr-HPV and thus it was not possible to calculate odds ratios. The final adjusted model controlled for self-reported age, current tobacco smoking, years of testosterone use, and HPV vaccination status; significance was determined at $p < 0.05$. Study methods were reviewed and approved by the Institutional Review Board at Fenway Health, Boston, MA, in accordance with the Helsinki Declaration of 1975, as revised in 2000.

RESULTS

A total of 150 participants were enrolled in the parent study. Eighteen participants who did not have valid results for provider-collected specimens were excluded: 3 participants did not complete the provider test; for 6 participants there was a lab error with the provider test; and 9 of the provider samples could not be assayed due to low cellular content, resulting in an analytic sample of 132 for this secondary analysis.

As shown in Table 1, the majority of participants (90.1%) were between the ages of 21 and 34; were white (75.8%), non-Hispanic (9.5.9%); and had a binary gender identity (75.8%). More than half of the sample had received a 4 year college degree or more (59.1%); 75.8% were employed full or part time; and only 13.6% reported being unstably housed in the past 12 months. The majority of the sample identified as gay, bisexual, queer, or questioning (87.1%). Participants reported having partners of different genders, with the most commonly reported partners in the past 12 months being cisgender women (61.4%), followed by cisgender men (42.4%) and gender non-conforming people who were assigned female sex at birth (20.5%). Only 1 participant was HIV positive, which was confirmed via medical records.

As shown in Table 2, the overall prevalence of cervical hr-HPV in the sample was 15.9% (21/132). Nearly half of sexually active participants reported no penile sex in the past 12 months (48.5%); while 37.9% reported receptive vaginal sex with a penis and 6.8% reported penile sexual contact, but not receptive vaginal sex. A total of 30% of those who reported receptive vaginal sex tested positive for hr-HPV compared to 11.1% of those who had penile contact, but not receptive vaginal sex; 7.8% of those sexually active participants who did not have penile sex of any kind; and 0% of those who did not have sexual contact in the past 12 months. The mean participant age was 27.8 (SD = 5.7), with those with a positive hr-HPV DNA test having a slightly higher mean age (28.9 [SD = 5.9]) than those without hr-HPV (27.8 [SD = 5.7]). The mean number of years that participants were on hormones was 4.4 (SD = 4.4), with those with a positive hr-HPV DNA test having a slightly higher mean duration (5.4 [SD = 4.8]) than those without HPV (4.2 [SD = 4.3]). More than half of participants reported receiving at least 1 dose of the HPV vaccine (56.5%), with 14.9% of those who reported receiving the vaccine testing positive for HPV. Of the 21.4% of the sample that currently smoked tobacco, 28.6% tested positive for hr-HPV, compared to 12.6% of those who do not currently smoke tobacco.

As shown in Table 3, participants reporting receptive penile vaginal sex with any of their most recent 3 sexual partners in the past 12 months had more than 5 times greater odds of current hr-HPV infection than those sexually active participants reporting no penile sex of any kind during this timeframe (OR=5.06; 95% CI=1.69–15.12; p=0.01). After adjusting for age, current tobacco use, years of testosterone use, and HPV vaccination status, results were nearly identical (OR=5.23; 95% CI=1.61–17.02; p<0.01). There was no significant difference in the odds of hr-HPV infection between those sexually active participants reporting no penile sexual contact and those reporting other types of penile sex (i.e. non-vaginal-receptive sex).

DISCUSSION

This formative secondary analysis found that self-reported recent vaginal receptive sex with a penis was associated with a more than 5-fold increase in the odds of current cervical hr-HPV infection, as measured by a provider-collected cervical specimen, in comparison to those who were sexually active but reported no recent penile sexual activity of any kind. Findings were similar between the unadjusted and adjusted analyses. Prior study of this association in TM or cisgender women has been limited. One cross-sectional study of sexual minority women as young as age 17 found lower rates of infection with grouped hr-HPV subtypes 51, 52, 55, and 58 in those with exclusive lifetime sex with women as compared to those with a mix of male and female sexual partners in the past year. (30) Another study of sexual minority women as young as 19 found a lower rates of unclassified HPV infection in those with exclusive lifetime female partners than in those with a mix of male and female partners in the past year, and a positive association between any HPV infection (including non-oncogenic strains) and sex with men in the past two years. (31) An analysis of cisgender women participating in the NHANES study between years 2002–2011 who provided a self-collected vaginal probe testing for any strain of HPV found those reporting a lesbian sexual identity to have an odds ratio in an adjusted analysis of 0.38 compared to those reporting a heterosexual identity. (32) A study of a mixed-HIV status cohort of both heterosexual and sexual minority cisgender females found that no sexual contact with a (presumably cisgender) male in the past 5 years (but with at least 1, presumably cisgender, female sex partner in this time period) had an odds ratio of 0.48 for any strain of cervical HPV and 0.49 for any abnormal cervical cytology (ASCUS or worse) as compared to women who did have at least 1 (presumably cisgender) male partner in the past 5 years. (33) The current study expands this body of research to a TM patient population and explicitly considers penile sex acts instead of simply asking about the gender of sexual partner and/or sexual orientation measures. We also limited our outcome variable to the 13 strains known to be oncogenic for cervical cancer. These methods improve on limitations of these previous studies, given that sexual behavior can vary regardless of sexual orientation, in particular when considering partners who are also transgender, which may result in, for example, a lesbian having sex with a transgender woman who has a penis.

In addition to supporting the inclusion of transgender men specifically in cervical cancer screening guidelines, we hope that our study will support future population-based analyses to explore a more tailored approach to cervical cancer screening in TM, by incorporating factors such as lifetime sexual behaviors, age, tobacco use, HIV, and HPV vaccination history. Potential benefits of an individualized approach could include lengthened screening intervals or even early (i.e., before age 65) termination of screening, reducing both resource utilization as well as the physical and emotional distress associated with ongoing repeated screenings and potential false positives in those TM at lowest risk. Conversely, TM at average or elevated risk who have previously been reluctant to undergo screening, or have believed that as a non-cisgender/non-heterosexual person they were not at risk, may be more likely to engage in screening once they are aware of their individualized risk. More than half (57%) of our participants reported prior HPV vaccination, however the number of doses received was not recorded and these data are subject to considerable recall bias. (34)

Interestingly, a similar proportion of participants reporting at least 1 prior HPV vaccination dose tested positive for hr-HPV as did in the group reporting no prior vaccination (14.9% vs. 15.9%).

Findings of this formative secondary analysis should be considered in the light of several limitations. Our sample had high rates of sexual activity, and depended on recall of sexual behaviors in the past 12 months for only a maximum of 3 partners due to the wording of the questionnaire on the parent study. At the same time, the further back one goes into self-reporting sexual history, there is an increasing risk of recall bias. Furthermore, most cervical hr-HPV infections resolve within a relative short time course without intervention, suggesting that recent sexual activity is more predictive of current infection than is remote history. (35) Analysis of hr-HPV infection risk by sexual behavior was not the primary outcome measure of the parent study, and as such, detail on sexual behaviors beyond those with the most recent 3 partners in the past 12 months was not collected; the nature of reported non-vaginal-receptive penile sex (i.e. oral, anal, both, other acts) was also not collected. These limitations are rooted in the study and questionnaire design of the parent study. The cross-sectional nature limits ability to establish causation. The small sample size in the group reporting penile sexual contact, but not receptive vaginal sex specifically, does not allow for power to determine if that group has elevated risk of hr-HPV or not. We did not identify the specific subtype of hr-HPV for each participant, recognizing that subtypes 16 and 18 confer a higher risk than the 11 other subtypes implicated in cervical cancer. It is noteworthy that 15.9% of participants in this sample, including 6.9% (5/72) of those sexually active participants reporting no penile sexual contact of any kind in the past year, were positive for hr-HPV. Even among those with no penile contact in the past year, our sample may overestimate the prevalence of hr-HPV in some groups at lowest risk. Firstly, a higher prevalence overall is expected in this relatively young cohort. (35) Primary screening for hr-HPV in clinical settings is not recommended for this age group. Second, participants were recruited into a study of cervical cancer screening and sexual health. It is possible that people who would choose to enroll in such a study are more likely to be sexually active in general, and some of these participants may have acquired hr-HPV through penile sex more than 1 year ago, but within a recent enough time frame that their hr-HPV infection did not clear. Thirdly, It is also possible that these (or any of our) participants acquired hr-HPV through non-penile routes such as oral, digital, or vaginal-vaginal routes. All of this said, the finding of a significant difference in rates of infection based on measures of penile sexual behavior stands as relevant on its own, and there may be some TM (as well as cisgender women) who have either never had sexual contact of any kind, or who have had contact remotely enough and with interval negative screening, that increased intervals or early termination of screening could be found to be appropriate after further study of this matter. This consideration is supported by the finding that none of the 8 participants with no sexual contact of any kind in the past year had a current hr-HPV infection. In the lack of such data, TM should continue to receive a recommendation for cervical cancer screening as with cisgender women with a cervix, both in published guidelines and in the exam room. With regards to our choice to calculate odds ratios rather than relative risk, we recognize that that for non-rare outcomes, odds ratios overestimate relative risks. Realistically, this concern is only problematic when the odds ratios are interpreted as relative risk. We are careful in our

interpretation of the data and discuss the findings in terms of increased odds in order to avoid conflation of odds ratios equating to relative risk. (36) We were not able to adjust for HIV status, since only 1 participant was HIV-positive; this participant was negative for cervical hr-HPV, reporting no penile sex in the past 12 months and were currently on anti-retroviral therapy.

CONCLUSION

Sexual behavior, specifically vaginal-receptive penile sex in the last 12 months, was associated with a five-fold increased odds of cervical high-risk HPV infection in a sample of TM ranging from age 21 to 50. Recognizing that our study has limitations, we feel that our formative, secondary analysis highlights the importance of including TM in cervical cancer screening guidelines and programs, and demonstrates a need for population level study to better describe the association between risk factors, such as sexual behavior, and cervical hr-HPV infection.

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Table 1.

Demographics of a sample of trans masculine adults (N = 132).

Age, categorical	N	%
21–24	44	33.3
25–29	52	39.4
30–34	23	17.4
35–39	9	6.8
40–50	4	3.0
Race		
White	100	75.8
American Indian or Alaska Native	0	0.0
Asian	7	5.3
Native Hawaiian or Pacific Islander	1	0.8
Black or African American	4	3.0
More than one race	20	16.4
Hispanic or Latinx Ethnicity		
Not Hispanic or Latinx	117	95.9
Hispanic or Latinx	13	10.7
Not reported	2	1.6
Gender Identity		
Binary	101	76.5
Non-Binary	31	23.5
Education - Highest Level		
High School or equivalent	14	10.6
Some college (1–3 years)	40	30.3
College graduate (4 year college degree)	39	29.5
Graduate school	39	29.5
Employment - Current		
Unemployed	28	21.2
Employed part time	40	30.3
Employed full time	60	45.5
Not reported	4	3.0
Unstably Housed - Past 12 Months		
No	114	86.4
Yes	18	13.6
Sexual Orientation		
Straight/heterosexual	17	12.9
Gay, bisexual, queer, questioning	115	87.1
Partnered/In a Relationship - Current		
No	50	37.9
Yes	82	62.1
Gender of Partners—Past 12 months**		

Age, categorical	N	%
Cisgender man	56	42.4
Cisgender woman	81	61.4
Transgender man	22	16.7
Transgender woman	17	12.9
Gender non-conforming - Male assigned sex at birth	7	5.3
Gender non-conforming - Female assigned sex at birth	27	20.5
HIV Status		
Positive (confirmed)	1	0.8
Negative	130	98.5
Confirmed	110	83.3
Self-report	20	15.2
Don't Know	1	0.8

**
Not mutually exclusive

Note. All variables are based on self-report. For most participants, HIV status was confirmed via rapid HIV testing, however, the status of the HIV positive participant was verified via medical records. Notably, 21 participants did not complete the rapid HIV test, but self-reported being HIV negative; and 1 participant did not complete the rapid test and self-reported that they did not know their HIV status.

Table 2. Descriptive statistics of study variables overall and stratified by cervical hr-HPV status (N = 132).

OUTCOME	Total Sample N= 132			Provider-Collected Cervical Hr-HPV DNA**		
	N	%		Yes	No	
Provider-Collected Cervical HPV DNA						
Positive	21	15.9				
Negative	111	84.1				/
INDEPENDENT VARIABLE						
Sexual Behavior - Past 12 months						
Yes, receptive penile vaginal sex	50	37.9	15	30.0	35	70.0
Yes, penile sex, but not receptive vaginal	9	6.8	1	11.1	8	88.9
No penile sex	64	48.5	5	7.8	59	92.2
No sexual contact	8	6.1	0	0.0	8	100
Not reported	1	0.8	0	0.0	1	100
COVARIATES						
Age	Mean	SD	Mean	SD	Mean	SD
Range (21 – 50 years)	27.8	5.7	28.9	5.9	27.8	5.7
Years on Hormones						
Range (0 – 14 years)	4.4	4.4	5.4	4.8	4.2	4.3
HPV Vaccine (n = 131)	N	%	N	%	N	%
Yes	74	56.5	11	14.9	63	85.1
No	46	35.1	6	13.0	40	87.0
Don't know	11	8.4	4	36.4	7	63.6
Currently Smokes Tobacco (n = 131)						
Yes	28	21.4	8	28.6	20	71.4
No	103	79.4	13	12.6	90	87.4

** The statistics for the stratified analyses reflect percentages and means/standard deviations (SD) for the row.

Note. Sexual behaviors were self-reported and inclusive to a maximum of last 3 sex partners in the past 12 months.

Bivariate and adjusted logistic regression analyses examining the association between sexual behavior and cervical HPV in a sample of trans masculine adults (N = 123).

Table 3.

Sexual Behavior	Provider-Collected Cervical hr-HPV DNA			Adjusted Model		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Yes, receptive penile vaginal sex	5.06	1.69–15.12	0.01	5.23	1.61–17.02	<0.01
Yes, penile sex, but not receptive vaginal	1.48	0.15–14.28	0.74	1.42	0.13–15.04	0.77
No penile sex	Referent	---	---	Referent	---	---

Note. The 8 participants with no sexual contact and 1 participant who did not report their sexual behavior in the past 12 months were removed from the logistic regression analyses due to low cell count (i.e., 0 tested positive for cervical hr-HPV) resulting in an analytic sample of N = 123. CI = Confidence Interval; Adjusted for age, current tobacco use, years of testosterone use, and HPV vaccination status. Groups were defined by questionnaire design in the parent study; non-receptive penile vaginal sex was not further defined.